Relating extracellular diffusivity to cell size distribution and packing density as applied to white matter

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Introduction. What can the diffusion coefficient D_e of the extracellular (EC) water tell us about the packing geometry of cells? The answer to this question could help reveal clinically relevant morphological changes in disease, such as the degree of cell swelling, shrinkage or loss, or change in their packing geometry. Unfortunately, relating the long-time limit of the diffusion coefficient to the packing geometry has been a notoriously difficult problem. An equivalent problem of finding the dielectric function, or the electrical conductivity, of a suspension of "grains" in a "matrix" goes back to the mid-19th century[1,2], and has been a testing ground for effective medium approaches[3–8]. They work well for small volume fractions of the grains[1–6], or when the properties of the grains and of the matrix are similar[7,8]. For the physiologically relevant tight packing of practically impermeable cells, these approaches fail: the Hashin-Shtrikman bounds[9] and the Bruggeman-Sen solution[5,6] give only order-of-magnitude estimates, with ~100% errors in the physiologically relevant range of EC water fraction φ~0.2−0.5 (Fig. 1). Technically, as each grain (cell) strongly disturbs the diffusion paths, and their mutual effects are important due to a tight packing, there seems no obvious "small parameter" to control the convergence of any perturbative expansion. Yet, practically, addressing this challenge is very important, as the EC diffusivity D_e in the space between impermeable axons is a relatively straightforward parameter obtained from a two-compartment fit of the diffusion signal in white matter (WM) transverse to the fiber, measured at long diffusion times with the relatively small gradients available in clinical settings.

Methods. Here we develop a new analytical approach to this problem, which for the first time displays quantitative agreement with Monte Carlo (MC) simulations of the two-dimensional diffusion restricted by randomly packed impermeable disks whose size distribution reflects the measured axonal diameter distribution[10]. This geometry applies to quantifying white matter WM fiber integrity: Axons are modeled as parallel impermeable cylinders (disks in the plane transverse to fiber), their packing affected by either axonal loss (random removal of the disks), or demyelination (disk shrinkage). Fig. 1 shows the MC-simulated tortuosity $\Lambda = D_0/D_e$, with D_0 the free water diffusivity, together with results of our analytical modeling.

Our key idea is in the accounting for the distribution of axon sizes. As the axonal size distribution[10] has both a peak (representing many *small* similar-size axons) and a long tail (a few *large* axons), we approximate the disk size distribution by **two populations**: "small", '*s*' (of the same size), and "large", '*l*', with the ratio $\xi = \psi_l/\psi_s$ between their volume fractions being the only adjustable parameter characterizing the distribution.

Results. We consider the effect of small disks first, "homogenizing" at the scale exceeding their size, and then use the reduced diffusivity of population '*l*' to describe the further restriction to diffusion caused by rare large disks. In this way, the "small parameter" for the large disks becomes their relatively small fraction ψ_l. The challenge still remains to model the restriction caused by tightly packed small disks. Remarkably, we find that the effect of small disks randomly placed in-between the large ones is well captured locally by the exact solution[11] for a *square lattice* of disks. We focus on the EC conductivity $\sigma(\varphi)$ assuming the EC space filled with material with $\sigma_0 \equiv 1$; the EC tortuosity[7] $\Lambda = D_0/D_e = \varphi/\sigma(\varphi)$. The openings between small disks form a "resistor network"[12], which we treat locally as a square lattice made of "conductances" $\sigma_s = \sigma_\square(\psi_s/(1-\psi_l))$, where $\sigma_\square(\psi)$ is the exact conductivity[11] of a square lattice of identical nonconducting disks with fraction ψ. Effective medium treatment of adding large disks in the background of σ_s yields $\sigma = \sigma_\square(\psi_s/(1-\psi_l))\cdot(1-\psi_l)^2$, the black curve in Fig. 1. Using this two-stage approach, our tortuosity is clearly much closer to the MC results than that of earlier approaches[5–7] given by $\sigma = \varphi^2$ and $\Lambda = 1/\varphi$ (red dashed line). In Fig. 1, we took $\xi = 3{:}5 = 0.6$. This corresponds to large axons with diameter exceeding ~2μm,[10] contributing $\psi_l/\psi = \xi/(1+\xi) \approx 38\%$ of the net axonal volume $\psi = \psi_s + \psi_l = 1-\varphi$.

Demyelination shrinks both types of axons (in simulations, we chose shrinking of all disks by a common factor $\lambda > 1$). The conductivity of population '*s*' becomes $\sigma_s \to \sigma_\square(\psi_s/\lambda^2(1-\psi_l))$. The large disks are now substituted by disks with impermeable core of radius R/λ, coated by a shell between R/λ and R with free conductivity σ_0. Each such disk is equivalent to that with conductivity $\sigma_l = \sigma_0\cdot(\lambda^2-1)/(\lambda^2+1)$; filling in the space with these disks up to the volume fraction ψ_l using the approach[5–7], we obtain the magenta line in Fig. 1 with no extra free parameters (ξ fixed to 0.6).

Axonal loss: In our MC simulations, we choose to remove disks at random irrespective of their radius, preserving the shape of their size distribution. The loss reduces the relative fraction $f_s = \psi_s/\psi_{s,0}$ of small disks (where $\psi_{s,0}$ and $\psi_{l,0}$ are disk fractions before removal), and is treated[12] as the substitution of randomly chosen orthogonal bonds of a square lattice by those with unit conductance, $\sigma_\square \to \sigma_0$, increasing $\sigma_s \to \sigma_s(f_s)$. The loss of large disks can be treated using the infinitesimal addition approach[5–7], by infinitesimally increasing the fractions f_0 and f_l of "holes" (filled with σ_0) and grains (with $\sigma_l = 0$), from 0 up to $\psi_{l,0}-\psi_l$ and ψ_l correspondingly, with fixed ratio df_0/df_l, in the background of $\sigma_s(f_s)$. The corresponding differential equation yields an implicit solution for $\sigma(\varphi)$, $\varphi = 1-\psi_s-\psi_l$:

$$\left(\frac{\sigma}{\sigma_s(f_s)}\right)^{\eta/2}\left(\frac{\eta\sigma+1}{\eta\sigma_s(f_s)+1}\right)^{(1-\eta)/2} = 1-\psi_{l0}\,,\quad \eta = \frac{f_l+f_0}{f_l-f_0} = \frac{\psi_{l0}}{2\psi_l-\psi_{l0}}\,,$$

shown by the blue line in Fig. 1, again with no extra free parameters (keeping the same ξ =0.6).

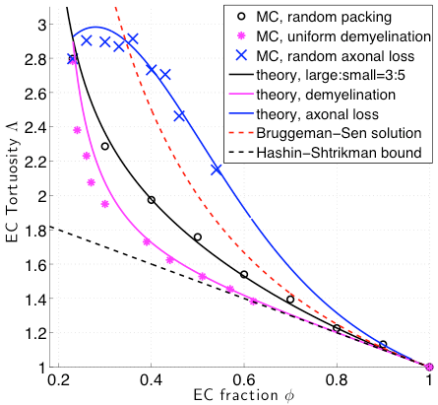

Figure 1: Comparison of our two-population model for the EC diffusion with MC simulations showing its advantage over existing approaches

Discussion. The unexpectedly good agreement between theory and MC simulations even for very tight packings suggests that the most relevant feature of the cell size distribution[10] is the relative contribution ξ of its tail (large axons) to its bulk (small axons), with the variation of sizes within those populations being less important. Our approach also explains the decoupling of axonal loss and demyelination in the EC diffusion: While demyelination sharply increases the "conductance" of the tightly packed population '*s*' leading to a sharp tortuosity drop, the axonal loss introduces isolated conducting "pockets" in the midst of poorly conducting bulk, resulting in a very slow initial conductivity increase and, thereby, the initial overall *decrease* of EC diffusivity $D_e \propto \sigma(\varphi)/\varphi$ in response to the increase of φ (Fig. 1). The decoupling of axonal loss and demyelination can allow one to differentiate between different kinds of WM damage. Our analytical approach extends onto the simultaneous demyelination and loss of small and/or large axons, and can be used to quantify subtle changes in WM structure in disease using clinically available low-*q* DWI metrics.

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